




ORIGINAL ARTICLE

The burden of subclinical cardiovascular disease in children and young adults with chronic kidney disease and on dialysis

Alexander D. Lalayiannis ¹, Charles J. Ferro ², David C. Wheeler³, Neill D. Duncan⁴, Colette Smith⁵, Joyce Popoola⁶, Varvara Askiti⁷, Andromachi Mitsioni⁷, Amrit Kaur⁸, Manish D. Sinha ⁹, Simon P. McGuirk¹⁰, Kristian H. Mortensen¹, David V. Milford¹⁰ and Rukshana Shroff¹

¹University College London Great Ormond Street Hospital Institute of Child Health, London, UK, ²University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, ³Department of Renal Medicine, University College London, London, UK, ⁴Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, UK, ⁵Institute of Global Health, University College London, London, UK, ⁶Department of Nephrology and Transplantation, St. George's University Hospital NHS Foundation Trust, London, UK, ⁷“P. & A. Kyriakou” Children's Hospital, Athens, Greece, ⁸Manchester University NHS Foundation Trust, Manchester, UK, ⁹Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK and ¹⁰Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

Correspondence to: Alexander D. Lalayiannis; E-mail: alex.lalayianis@nhs.net

ABSTRACT

Background. Cardiovascular disease (CVD) is a common cause of morbidity and mortality even in young people with chronic kidney disease (CKD). We examined structural and functional CV changes in patients <30 years of age with CKD Stages 4 and 5 and on dialysis.

Methods. A total of 79 children and 21 young adults underwent cardiac computed tomography for coronary artery calcification (CAC), ultrasound for carotid intima-media thickness (cIMT), carotid–femoral pulse wave velocity (cfPWV) and echocardiography. Differences in structural (CAC, cIMT z-score, left ventricular mass index) and functional (carotid distensibility z-score and cfPWV z-score) measures were examined between CKD Stages 4 and 5 and dialysis patients.

Results. Overall, the cIMT z-score was elevated [median 2.17 (interquartile range 1.14–2.86)] and 10 (10%) had CAC. A total of 16/23 (69.5%) patients with CKD Stages 4 and 5 and 68/77 (88.3%) on dialysis had at least one structural or functional CV abnormality. There was no difference in the prevalence of structural abnormalities in CKD or dialysis cohorts, but functional abnormalities were more prevalent in patients on dialysis ($P < 0.05$). The presence of more than one structural

Received: 23.4.2021; Editorial decision: 23.8.2021

© The Author(s) 2021. Published by Oxford University Press on behalf of the ERA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

abnormality was associated with a 4.5-fold increased odds of more than one functional abnormality (95% confidence interval 1.3–16.6; $P < 0.05$). Patients with structural and functional abnormalities [cIMT z-score > 2 standard deviation (SD) or distensibility < -2 SD] had less carotid dilatation (lumen:wall cross-sectional area ratio) compared with those with normal cIMT and distensibility.

Conclusions. There is a high burden of subclinical CVD in young CKD patients, with a greater prevalence of functional abnormalities in dialysis compared with CKD patients. Longitudinal studies are required to test these hypothesis-generating data and define the trajectory of CV changes in CKD.

Keywords: cardiovascular disease, carotid intima-media thickness, chronic kidney disease, coronary artery calcification, pulse wave velocity

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in young people with chronic kidney disease (CKD) [1]. Mineral dysregulation in CKD—mineral and bone disorder (CKD-MBD) is causally linked with calcium (Ca) and phosphate (P) deposition in the medial layer of the arteries [2], with an increase in arterial thickness and stiffening of the vessels [3–5]. Vascular damage and calcification may be present early in the course of CKD [6, 7] and progresses rapidly once dialysis is initiated [2]. It has been suggested that structural changes lead to arterial stiffness that in turn causes an increased left ventricular (LV) pressure load [6] and LV hypertrophy (LVH), but correlations between structural and functional vascular changes and factors associated with these changes have not been fully examined.

In a cohort of children and young adults < 30 years of age, we examined structural changes [including coronary artery calcification (CAC), cIMT and LV mass], functional changes (carotid distensibility and arterial stiffness) and evidence of CV remodeling. Our hypothesis was that young people with CKD Stages 4 and 5 and on dialysis would have a high prevalence of subclinical CVD. We also wanted to examine the association of structural changes and functional abnormalities in this age group. This study is part of a longitudinal, multicentre study examining bone and CV health in children and young adults with CKD. Young adults are included, as the skeleton continues to mineralize until the third or fourth decade of life [8], accruing Ca and perhaps acting as a 'buffer' to prevent vascular calcification. The baseline cross-sectional data relating to CV health are presented in this article.

MATERIALS AND METHODS

Study participants

This cross-sectional study included young people with CKD Stages 4 and 5 (including individuals receiving dialysis) from five paediatric and four adult nephrology units. Our inclusion criteria were age 5–30 years and CKD Stages 4 and 5 [estimated glomerular filtration rate (eGFR), by the Schwartz formula [9], < 30 mL/min/1.73 m²] or on dialysis. It is thought that the high Ca requirement of the growing skeleton may exert a buffering capacity, reducing the incidence of extraosseous calcification. As skeletal mineralization can continue until 30 years of age, when peak bone mass is reached, we have included young adults up to 30 years of age [8]. Cross-sectional data on bone health of this cohort have been published previously [10]. We excluded patients with a functioning kidney transplant and those who would not have tolerated the scanning procedures. Informed written consent was obtained from all parents or

caregivers and adult participants. Assent was obtained from children where appropriate. The study was approved by the local research ethics committees.

A total of 130 patients were identified and 112 agreed to participate. Twelve withdrew consent prior to taking part. A total of 100 children and young adults with CKD completed the study and were included in the analyses.

Investigations performed

Details on anthropometric measurements and serum biomarker collection have been published previously [10] and are described in detail in the [Supplementary Materials](#). Manual blood pressure (BP) was recorded at routine clinic visits or before a midweek haemodialysis session by a single investigator (A.D.L.) and expressed as z-scores, adjusted for age, sex and height [11]. Hypertension (HTN) was defined as a systolic BP (SBP) and/or diastolic BP (DBP) measurement above the 95th centile for age and height as per the 2016 European Society of Hypertension (ESH) guidelines [12].

Given the age range of our patients, all age-related measures (including CV measures) are presented as z-scores. The z-scores reflect normative changes due to age, height and sex and allow for comparison of the vascular measures across all age groups.

cIMT and distensibility. cIMT measurements were obtained by ultrasound according to the Mannheim consensus [13]. The mean cIMT was calculated as the average IMT measurements of both carotids 1–2 cm below the bifurcation using automatic software (Vivid iq, GE Healthcare, Chicago, IL, USA) and analysed offline in a blinded fashion. The M-mode was used for vessel systolic and diastolic diameter (see [Supplementary Materials](#) for detailed description). The mean wall cross-sectional area (WCSA), mean lumen cross-sectional area (LCSA) [14], their ratio (LCSA:WCSA; reflecting the ability of the vessel to dilate in relation to vessel wall thickening), distensibility coefficient (reflecting the functional properties of the carotid and its ability to distend with each cardiac cycle) were also calculated ([Figure 1](#)) [15]. cIMT measurements were expressed as z-scores according to Doyon et al. [15]. Adults' z-scores were calculated using interpolation of the difference between 17 and 18 years old (the annual increase of absolute cIMT each year to the age of 30 years was assumed to be the same as the increase from 17 to 18 years). For comparison, we also generated z-scores for adults using other healthy reference databases [16, 17] (see [Supplementary data, Table S2 and Figure S1A](#)).

Cardiac computed tomography. Coronary artery and valvular calcification were examined by computed tomography (CT; Somatom Force; Siemens, Munich, Germany or GE Discovery

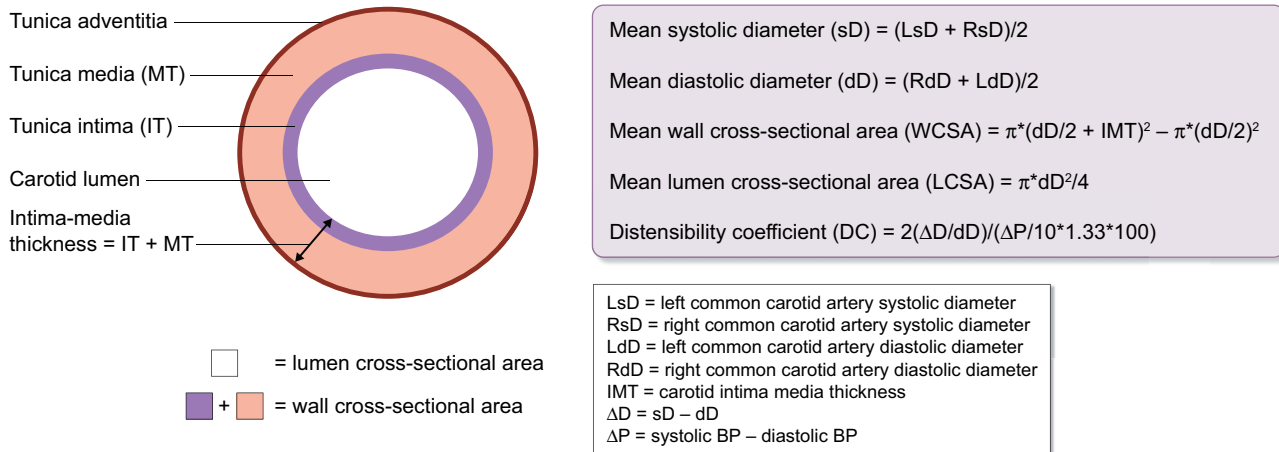


FIGURE 1: Schematic representation of the constituent parts of the carotid wall and the carotid measure equations [14, 15].

750HD, GE Healthcare) using the machines' standard Ca scoring protocol. Prospective echocardiography (ECG) triggering was used to obtain images in diastole. Calcification was expressed as the Agatston score [18] and analysed offline in a blinded fashion, confirmed independently by two observers (A.D.L. and K.H.M.) using Syngo Via software (Siemens, Cambridge, UK).

ECG. LV measures were collected from two-dimensional ECG. The LV mass was calculated according to the Devereux equation [19] and indexed to $height^{2.7}(g/m^{2.7})$ (LVMI) [7]. LVH was defined as sex- and age-specific LVMI above the 95th percentile as defined by Khoury *et al.* [20]. Evaluation of LV geometry (concentric versus eccentric hypertrophy) was done using the relative wall thickness (RWT) formula and normalized for age 10 years for participants <18 years old and age 46 years for participants >18 years old as described by de Simone *et al.* [21]. The 95th percentile cut-off values were used to define concentric geometry with 0.38 for children and 0.43 for adults [21].

cfPWV and pulse wave augmentation. Carotid–femoral pulse wave velocity (cfPWV) was measured with the Vicorder Oscillometric PWV device (SMART Medical, Moreton in Marsh, UK), which has been validated against applanation tonometry [22]. cfPWV results were expressed as z-scores based on reference values normalized for height and age [23]. Adult z-scores were calculated using interpolation of the values between 17 and 18 years old, similar to the cIMT z-scores (see [Supplementary Materials](#) for comparison with other healthy reference databases) [24, 25]. Pulse wave augmentation and augmentation index (AIx) were obtained with the same Vicorder device (SMART Medical).

CV abnormality scoring. We separated the CVD measures into structural (CAC, cIMT and LVMI) and functional (carotid distensibility and cfPWV) changes. We assigned 1 point for each measure above a z-score of 2 or above the 95th centile for all continuous data and into presence or absence of CAC based on

the Agatston score. The total structural and functional scores for each patient were calculated.

Statistics

All results are presented as the median with interquartile range (IQR) or number and percentage. Spearman rank testing was used for univariable correlations. Kruskal–Wallis analysis of variance was used for non-normally distributed data with Dunn's correction for multiple comparisons. Mann–Whitney U-tests were used for between-group non-parametric comparisons. A series of linear regression models were performed, with the CVD measures (cIMT z-score, LVMI, distensibility, carotid dilatation, PWV z-score and augmentation) as the dependent variables. All independent variables with univariable associations of $P \leq 0.15$ were included in the multivariable models (see [Supplementary Materials](#)). All regression models included the CKD stage as a binary measure (CKD Stages 4 and 5 or dialysis) nominal category split. Since z-scores are adjusted for age and sex, these were not included as a dependent variable. The association of structural and functional changes was expressed as odds ratios with 95% confidence intervals (CIs) and an associated P-value was calculated using Fisher's exact test. SPSS version 25 (IBM, Armonk, NY, USA) was used for all statistical analyses and GraphPad Prism (GraphPad Software, San Diego, CA, USA) was used to create figures. A two-sided P-value ≤ 0.05 was considered to indicate a statistically significant difference.

RESULTS

The demographics of the study population are shown in [Table 1](#). Dialysis participants were older [median 14.3 (IQR 11.1–22.0) versus 11.5 (6.8–13.6) years; $P = 0.002$], more likely to be Asian (29.9% versus 17.4%) or Black (23.4% versus 8.7%, respectively; $P = 0.03$) and more likely to have an underlying glomerular disease (16.9% versus 0%; $P = 0.001$).

Table 1. Patient characteristics

Patient characteristics	Total	CKD	Dialysis	Between group comparison (P-value)
Patients, n (%)	100	23 (23)	77 (77)	NA
Age (years)	13.82 (10.68–16.46)	11.46 (6.80–13.58)	14.25 (11.10–21.95)	0.002
5–18, n (%)	79 (79)	23 (100)	56 (73)	0.17
19–30, n (%)	21 (21)	0	21 (27)	NA
Female, n (%)	44	6 (26.1)	38 (49.4)	0.06
Race (Caucasian/Asian/Black/Other), n	52/27/20/1	17/4/2/0	35/23/18/1	NA
Height z-score	−1.09 (−1.93 to −0.36)	−0.84 (−1.6–0.04)	−1.42 (−2.02 to −0.43)	0.06
Weight z-score	−0.56 (−1.67–0.20)	−0.21 (−1.02–0.64)	−0.78 (−1.77–0.02)	0.02
BMI z-score	0.14 (−0.88–0.92)	0.52 (−0.66–1.28)	0.01 (−0.95–0.83)	0.06
SBP z-score	0.89 (0.03–1.67)	0.40 (−0.10–1.13)	0.96 (0.12–1.83)	0.02
DBP z-score	0.72 (−0.14–1.36)	0.50 (−0.18–1.11)	0.87 (−0.04–1.45)	0.30
Dialysis modality (HD/HDF/home HD/PD), n	44/14/3/16	NA	44/14/3/16	NA
P-binder therapy (Ca based/non-Ca based/both/none), n	39/23/5/33	16/1/0/6	23/22/5/27	NA
Anti-hypertensive therapy (ACEi, ARB/ β -blocker/Ca-channel blocker/diuretic/combination), n	1/0/1/2/4	0/0/0/0/0	1/0/1/2/4	NA
eGFR (mL/min/1.73 m ²)	NA	13.33 (9.72–18.05)	NA	NA
Years with eGFR <30 mL/min/1.73 m ²	5.58 (2.02–10.10)	3.68 (1.10–8.81)	5.63 (2.50–10.45)	0.09
Dialysis vintage (years)	2.51 (0.75–5.11)	NA	2.51 (0.75–5.11)	NA
Serum biomarkers				
Total Ca (mmol/L)	2.47 (2.37–2.56)	2.48 (2.43–2.53)	2.47 (2.35–2.58)	0.99
Ionized Ca (mmol/L)	1.21 (1.12–1.29)	1.22 (1.16–1.27)	1.20 (1.11–1.29)	0.46
P (mmol/L)	1.53 (1.30–1.87)	1.46 (1.32–1.60)	1.58 (1.29–1.90)	0.20
ALP (IU/L)	183.50 (116.80–267.50)	184.00 (156.00–227.00)	183.00 (102.50–285.50)	0.93
25(OH)D (nmol/L)	78.00 (37.55–113.80)	94.00 (71.00–144.00)	61.00 (36.00–106.70)	0.01
PTH (\times ULN)	$\times 3$ ($\times 1$ to $\times 10$)	$\times 1$ (< 1 to $\times 3$)	$\times 5$ ($\times 1$ to $\times 13$)	0.0005

Values are presented as median (IQR) unless stated otherwise. NA, not applicable; HD, haemodialysis; HDF, haemodiafiltration; PD, peritoneal dialysis; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ALP, alkaline phosphatase.

Table 2. Structural and functional CV measures in CKD and dialysis cohorts

Vascular measures	Total	CKD	Dialysis	Between group comparison (P-value)
Structural measures				
cIMT z-score	2.17 (1.14–2.86)	2.46 (1.04–2.76)	2.01 (1.14–2.94)	0.72
CAC, % (Agatston score range)	10 (0–412.6)	4.3 (0–6.4)	12 (0–412.6)	0.36
LVMI (g/m ^{2.7})	31.8 (28.0–37.6)	30.23 (23.51–33.44)	32.74 (29.48–42.48)	0.01
RWT	0.34 (0.29–0.40)	0.32 (0.29–0.38)	0.37 (0.30–0.44)	0.08
Functional measures				
Distensibility	−1.11 (−2.17 to −0.15)	−0.39 (−1.34–0.47)	−1.46 (−2.29 to −0.30)	0.009
cfPWV z-score	1.45 (−0.16–2.57)	0.61 (−0.78–2.23)	1.52 (0.28–2.81)	0.03
Augmentation (mmHg)	6.00 (4.00–10.00)	6.33 (4.17–9.5)	5.33 (3.33–10.67)	0.60
Aix (%)	15.83 (10.67–24.00)	16.00 (11.17–22.50)	13.67 (9.00–25.67)	0.73
Carotid dilatation (LCSA:WCSA)	3.06 (2.78–3.36)	3.22 (3.03–3.61)	2.98 (2.68–3.29)	0.006

Values are presented as median (IQR) unless stated otherwise. Investigations were performed in the entire cohort, except echocardiography, which was performed in 21/23 CKD patients and 62/77 dialysis patients.

As per the ESH guidelines, 28% of the cohort was hypertensive. HTN was more prevalent in patients on dialysis (33.8% versus 8.6%; $P = 0.03$). There was no difference between those with glomerular versus non-glomerular (38.5% versus 26.4%; $P = 0.51$) disease. About 8% of the cohort were on antihypertensive medication (Table 1), and of these, 50% had uncontrolled HTN.

Patients on dialysis had lower 25-hydroxyvitamin D [25(OH)D; 61 versus 94 nmol/L; $P = 0.01$] and higher parathyroid hormone (PTH) levels compared with CKD patients [$5\times$ versus $1\times$ the upper limit of normal (ULN); $P = 0.0005$; Table 1].

Vascular measures

The structural and functional vascular measures for the total cohort as well as the CKD Stages 4 and 5 and dialysis groups are summarized in Table 2.

Structural measures

cIMT. The cIMT z-scores were high across the entire study population and there was no evidence of a difference between

dialysis and CKD cohorts. Serum alkaline phosphatase (ALP) levels were correlated with cIMT z-scores ($r=0.26$, $P=0.009$). There were no independent associations of cIMT z-scores on multivariable analyses (Supplementary data, Tables S4–S7).

CAC. Ten participants (nine on dialysis and one with CKD) had CAC; the Agatston score ranged from 0.8 to 412.6. There were no significant correlations between the Agatston score and other vascular measures or serum biomarkers (Supplementary data, Tables S4–S6). There was no difference between those with CAC and those without in terms of age, time on dialysis or serum biomarkers, and the presence of CAC did not correlate with other vascular measures (Supplementary data, Table S8).

LVMI. LVMI was higher in dialysis patients compared with CKD patients ($P=0.01$). LVMI correlated with HTN ($r=0.39$, $P<0.001$) and distensibility ($r=-0.32$, $P=0.003$). On multivariable regression, LV ejection fraction ($\beta=-0.39$, $P=0.001$), CAC Agatston score ($\beta=0.25$, $P=0.02$) and HTN ($\beta=0.40$, $P<0.0001$) were independent associations of LVMI ($R^2=0.35$) (Supplementary data, Table S9).

A total of 21.7% of patients had an LVMI above the 95th centile. In the participants with LVMI above the 95th centile, 61.1% showed concentric hypertrophy with RWT above the 95th centile and 38.9% with eccentric hypertrophy. A total of 14.5% had RWT above the 95th centile. Of the patients with a high RWT, 58.3% had LVMI above the 95th centile. Therefore 41.6% showed evidence of cardiac remodelling without a significant increase in LVMI.

Functional measures

Carotid distensibility. The carotid distensibility z-score was lower in patients on dialysis compared with CKD [-1.46 (IQR -2.29 to -0.30) versus -0.39 (-1.34 – 0.47), $P=0.009$] (Table 2). The carotid distensibility z-score correlated with the number of years with an eGFR <30 mL/min/1.73 m² ($r=-0.22$, $P=0.03$), SBP z-score ($r=-0.25$, $P=0.01$), ionized Ca (iCa; $r=0.21$, $P=0.03$) and 25(OH)D ($r=0.28$, $P=0.006$) (Supplementary data, Tables S10 and S11). On multivariable analysis, the SBP z-score was the strongest independent predictor of distensibility ($\beta=-0.33$, $P=0.002$; Supplementary data, Table S12). Being on dialysis (versus being in CKD Stages 4 and 5) was also an independent predictor of reduced distensibility ($\beta=-0.22$, $P=0.03$, Model 1 $R^2=0.27$; Supplementary data, Table S12). When replacing the binary CKD/dialysis with years with an eGFR <30 mL/min/

1.73 m², this was also significant ($\beta=-0.26$, $P=0.01$, Model 2 $R^2=0.28$).

cfPWV and pulse wave augmentation. The median cfPWV z-score was 1.45 (IQR -0.16 – 2.57) and higher in dialysis than CKD patients (1.52 versus 0.61; $P=0.03$; Table 2). cfPWV z-scores correlated with SBP and DBP z-scores ($r=0.41$, $P<0.0001$ and $r=0.39$, $P<0.0001$, respectively), as well as the presence of HTN ($r=0.26$, $P=0.009$; Supplementary data, Tables S11 and S12). There were no independent associations of cfPWV z-scores on multivariable regression, with only the DBP z-score approaching significance ($\beta=0.26$, $P=0.056$; Supplementary data, Table S14).

There was no difference between dialysis and CKD Stages 4 and 5 for augmentation or AIx. Augmentation was associated with the DBP z-score ($r=0.22$, $P=0.03$) and HTN ($r=0.20$, $P=0.048$) (Supplementary data, Tables S10 and S11). The presence of HTN was an independent association of augmentation ($\beta=0.28$, $P=0.02$, $R^2=0.05$) (Supplementary data, Table S15). AIx had no correlates or independent associations on multivariable regression.

Prevalence of abnormal structural and functional CV measures

The percentages of CKD Stages 4 and 5 and dialysis patients with structural and functional measures >2 standard deviation (SD) are summarized in Table 3. There was no difference in the prevalence of structural abnormalities between the CKD and dialysis cohorts ($P=0.43$). Patients on dialysis had a higher functional abnormalities score compared with the CKD cohort ($P=0.046$). The odds of having any structural or functional abnormality were 17.3 times higher in the dialysis compared with the CKD cohort [95% CI 5.28–53.52; $P<0.0001$; sensitivity 64.00% (95% CI 44.52–79.75), specificity 90.67% (95% CI 81.97–95.41)]. Overall, the presence of more than one structural abnormality increased the odds of more than one functional abnormality by 4.5-fold [95% CI 1.27–16.59; $P=0.045$; sensitivity 88.76% (95% CI 80.54–93.78), specificity 36.36% (95% CI 15.17–64.62)].

The role of arterial dilatation

Carotid dilatation (LCSA:WCSA ratio) was lower in the dialysis cohort compared with the CKD Stages 4 and 5 cohort (2.98 versus 3.22; $P=0.006$; Table 2) and correlated with dialysis vintage ($r=-0.23$, $P=0.045$), cIMT z-score ($r=0.36$, $P<0.0001$), HTN ($r=0.25$, $P=0.01$) and distensibility ($r=0.28$, $P=0.004$;

Table 3. Structural and functional abnormalities scores depicting the proportion of CKD and dialysis patients with vascular measures >2 SDs from the mean or the 95th centile

Vascular measures	CKD, % (n = 23)	Dialysis, % (n = 77)	Between-group comparison (P-value)
Structural abnormalities			
cIMT	60.87	50.65	0.47
CAC (presence of)	4.35	11.69	0.44
LVMI, g/m ^{2.7}	4.76	27.42	0.03
Total structural score 0/1/2/3	39.13/52.17/8.70/0.0	32.47/51.95/14.29/1.30	0.43
Functional abnormalities			
Distensibility (less than -2 SD)	13.04	36.36	0.04
cfPWV	30.43	38.96	0.47
Total functional score 0/1/2	60.87/34.78/4.35	37.65/49.35/13.00	0.046

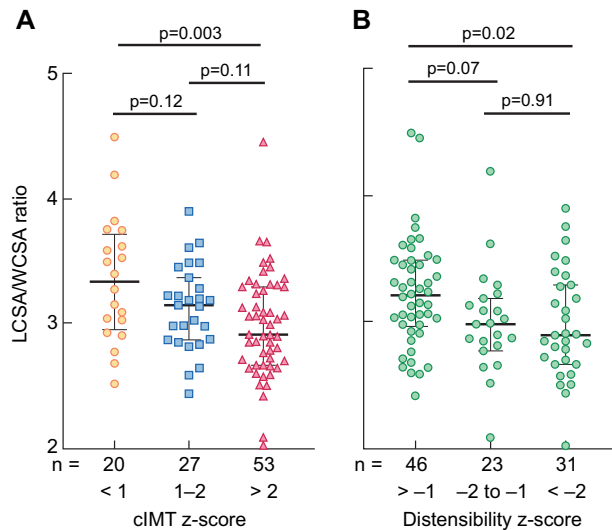


FIGURE 2: LCSA:WCSA ratios for patients according to cIMT z-scores and distensibility z-scores. Lines depict median and IQR.

Supplementary data, Table S11). Distensibility and HTN were independent associations ($\beta = 0.29$, $P = 0.004$ and $\beta = 0.25$, $P = 0.03$, respectively; $R^2 = 0.19$; Supplementary data, Table S13).

The carotid dilatation was lower in patients with cIMT z-scores >2 SD compared with <1 SD [2.91 (IQR 2.66–3.29) versus 3.33 (2.95–3.72); $P = 0.003$] (Figure 2A). The same was true when comparing patients with cIMT z-scores <2 SD and >2 SD [3.18 (IQR 2.89–3.49) versus 2.91 (2.66–3.29); $P = 0.006$]. Changes in carotid dilatation were not attributable to higher WCSA or lower LCSA in isolation, as there was no difference in LCSA or WCSA between those with cIMT <1 , 1–2 and >2 SD for either measure ($P = 0.07$ and $P = 0.76$, respectively).

The carotid dilatation was significantly lower in patients with impaired arterial distensibility (<-2 SD) than those with distensibility >-1 SD [2.89 (IQR 2.66–3.29) versus 3.21 (2.96–3.49); $P = 0.02$] (Figure 2B), without corresponding changes in cIMT z-score [1.80 (IQR 1.14–2.93) versus 2.31 (0.99–2.88), $P = 0.82$]. Carotid dilatation was greater in those with HTN compared with those without HTN [3.30 (IQR 2.94–3.51) versus 2.98 (2.77–3.27), $P = 0.02$]. There was no difference in carotid dilatation between those with LVMI above the 95th centile and those without [3.14 (IQR 2.72–3.39) versus 3.08 (2.82–3.38); $P = 0.72$].

DISCUSSION

In this study we showed that subclinical CV abnormalities/changes are significantly prevalent in children and young adults with stages CKD Stages 4 and 5 and on dialysis, with up to 69.5% of CKD and 88.3% of dialysis patients having at least one structural or functional CV abnormality. This is the first study in a young CKD cohort, to our knowledge, examining structural and functional CV abnormalities, with a comprehensive panel of surrogate vascular measures including CAC. The prevalence of structural abnormalities did not differ between the non-dialysis and dialysis cohorts, but functional abnormalities were more prevalent in patients on dialysis. The presence of more than one structural abnormality increased the odds of more than one functional abnormality 4.5-fold. These data highlight the burden of subclinical CVD even in a young cohort of CKD Stages 4 and 5 and dialysis patients, stressing the importance of preventative strategies to halt the development or attenuate the

progression of CVD in CKD. Also, our study suggests that there may be a temporal association between early structural changes that progress to functional CVD abnormalities when potential compensatory mechanisms, such as carotid dilatation that preserves vessel patency even in the presence of wall thickening, are overwhelmed; these hypothesis-generating data will be explored in future longitudinal studies.

Substantial structural CV changes were evident in our cohort, with a high cIMT z-score in 53% and the presence of CAC in 10%. The prevalence of CAC in our cohort is lower than in previously published studies [2, 26, 27], but the prevalence of CAC remains a concern, as it has been shown to be a significant predictor of major adverse CV events and mortality, due to its direct effect on myocardial perfusion [28, 29], and once coronary calcification is present, it progresses rapidly. In this young cohort, patients on dialysis had higher age-adjusted vascular stiffness measures compared with the CKD cohort, indicating a greater prevalence of functional CVD. Both the carotid distensibility z-score as well as cfPWV z-score were above normal, implying that arterial stiffness was present in multiple vascular beds. While dialysis *per se* was independently associated with reduced distensibility, the years with a low eGFR (<30 mL/min/1.73 m²) was also an independent predictor of vessel stiffness, implying cumulative CV damage due to prolonged exposure to the uraemic milieu or that dialysis treatment may be deleterious. Aortic stiffness, as assessed by cfPWV, is an independent predictor of progression to dialysis and mortality in adult patients with CKD Stages 2–5 [30, 31].

We examined the structural and functional abnormalities separately, but the carotid dilatation (LCSA:WCSA ratio) offers a way of assessing structural and functional changes simultaneously. In our cohort, we showed that the carotid dilatation was lower in patients with high cIMT z-scores (>2 SD), but this was not due to a WCSA increase or an LCSA decrease alone. In fact, the LCSA did not differ between patients with cIMT z-scores of <1 , 1–2 and >2 SD. This raises the possibility that vessel patency is maintained by arterial dilatation as a compensatory mechanism for increased cIMT early in the process of arterial wall thickening, but that there exists a physical limit beyond which the capacity to dilate is overwhelmed. This is also demonstrated by the fact that the patients with poor carotid distensibility (z-score <-2 SD) had lower dilatation compared with patients with distensibility >-1 SD. The cIMT z-scores did not correlate with distensibility, indicating that the dilatation is a separate mechanism to the structural changes that occur. The arterial tree functions as a network of conduits, but it also acts as a temporary reservoir for the cardiac output [32]. The elastic properties of the arteries are due to the presence of elastin fibres. However, elasticity of the vessels is a non-linear property. At lower pressures, elastin-distensible fibres bear the tension, but at higher pressures, elasticity is sustained by collagen fibres (which are less extendible), making the vessel progressively stiffer [33]. This loss of distensibility is compensated for, in part, by dilatation of the arteries [33]. Above a certain threshold, at which distensibility is significantly decreased and dilatation is no longer sufficiently compensatory, an increase in PWV is seen. Arterial stiffening is also observed in the otherwise healthy ageing population [34] and in disease groups, such as William's syndrome, wherein elastin mutations affect the elastic extracellular matrix structure of the arteries [35]. Even in people with essential HTN, arterial eutrophic remodelling (increasing LCSA:WCSA with static WCSA), highlighting the dilatation in the context of sustained increased pressure, is associated with vessel stiffness and functional changes [36]. In

CKD, arterial stiffening is likely to be a multifactorial process caused by the uraemic environment, inflammation, oxidative stress and HTN, which all contribute to direct vascular damage [32]. The subsequent remodelling is hypertrophic, with increasing WCSA due to cIMT changes, as well as increasing LCSA:WCSA [37]. In turn, arterial stiffness increases the cardiac afterload, leading to LV remodelling [38]. The structural changes, such as cIMT increase and subsequent stiffening, begin in early CKD stages, and functional abnormalities due to remodelling occur in later stages with progression of CVD [6]. This may be evident in our cohort, as years spent with a low eGFR was a significant negative predictor of carotid distensibility.

Few other studies have examined structural and functional abnormalities separately in young people with CKD [39]. Litwin *et al.* [6] showed that there is an increase in IMT in the early stages of CKD preceding arterial stiffening. After renal transplantation, the cIMT potentially decreases, whereas the arterial dilatation does not, suggesting that the structural and functional changes are associated but not inextricably linked [6]. In adult patients with mild to moderate CKD, carotid diameter was larger than age- and sex-adjusted hypertensive and non-hypertensive controls [36]. The same was true of carotid compliance (compliance = arterial cross-sectional area change/local pulse pressure) (CKD versus hypertensive patients, $P < 0.001$) but carotid distensibility was lower, indicating that, in this study by Briet *et al.* [36], an increase in arterial diameter appears to serve as a compensatory mechanism to maintain perfusion. This temporal association of structural changes with functional abnormalities needs to be elucidated further, and a longitudinal study is currently under way with this aim.

In our cohort, a fifth of patients had LVMI above the 95th centile (21.7%), of which almost 40% had eccentric hypertrophy. More than 40% of patients with evidence of cardiac remodelling did not meet the criteria for LVH. Abnormal LV geometry is common in CKD [40], with impaired systolic mechanical function in a significant proportion [41]. In the Cardiovascular Comorbidity in Children with CKD study, a prospective multi-centre longitudinal follow-up of >700 children with CKD Stages 3–5 and on dialysis, a third of patients had LVH, but 26% of the cohort showed cardiac remodelling even with normal LV mass [7]. In a substudy of 272 children, detailed echocardiographic analysis showed 55% had LVH and concentric hypertrophy was present in 65% of those with LVH. Despite the high prevalence of cardiac geometric remodelling, all the patients had a normal ejection fraction (>56%); the authors speculate that concentric hypertrophy may not be a compensatory effect but rather a reflection of structural alterations of the myocardium showing impaired contraction [41].

Our study is limited by the absence of ambulatory assessment of BP, as we performed single office-based manual BP measurements in the clinic or prior to a dialysis session. Even though masked HTN is unlikely if BP is in the low-normal range [42], 28% of our cohort was defined as hypertensive. The cross-sectional design of the study does not allow us to explain the role of HTN in any detail as a cause or effect of structural and functional changes in this cohort. The likely bidirectional effect of HTN on arterial stiffness in the general as well as in the CKD population has been explored extensively [43].

For this cross-sectional analysis we used only single time-point measurements of serum biomarkers, which may explain why we did not find associations between CKD-MBD biomarkers and vascular measures. The longitudinal follow-up study of this cohort will include the time-averaged measurements of

routinely measured serum biomarkers as well as research biomarkers of CVD in CKD. All the young adults in our study were on dialysis, so CVD changes in adult-onset CKD could not be studied. The z-scores were used to express all vascular measures, to enable comparison across the age range. Further longitudinal studies are in progress to better understand the temporal association between structural and functional CVD measures and risk factors associated with their progression.

In summary, this cross-sectional study shows a high prevalence of subclinical CVD in children and young adults with CKD and on dialysis. The prevalence of structural changes including cIMT increase and CAC was comparable in CKD and dialysis cohorts, but indices of arterial stiffness were higher in patients on dialysis, perhaps having developed when compensatory mechanisms such as arterial dilatation are overwhelmed. Further longitudinal studies are required to define the trajectory of CV changes in children and young adults with CKD in order to identify early intervention strategies.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](https://ckj.oup.com/ckj) online.

CONFLICT OF INTEREST STATEMENT

All authors have declared no conflicts of interest. The results presented in this article have not been published previously.

REFERENCES

- Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. *J Am Soc Nephrol* 2012; 23: 578–585
- Shroff RC, Donald AE, Hiorns MP *et al.* Mineral metabolism and vascular damage in children on dialysis. *J Am Soc Nephrol* 2007; 18: 2996–3003
- Shroff RC, McNair R, Figg N *et al.* Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. *Circulation* 2008; 118: 1748–1757
- Shroff RC, McNair R, Skepper JN *et al.* Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. *J Am Soc Nephrol* 2010; 21: 103–112
- Shroff R, Long DA, Shanahan C. Mechanistic insights into vascular calcification in CKD. *J Am Soc Nephrol* 2013; 24: 179–189
- Litwin M, Wuhl E, Jourdan C *et al.* Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. *J Am Soc Nephrol* 2005; 16: 1494–1500
- Schaefer F, Doyon A, Azukaitis K *et al.* Cardiovascular phenotypes in children with CKD: the 4C study. *Clin J Am Soc Nephrol* 2017; 12: 19–28
- Weaver CM, Gordon CM, Janz KF *et al.* The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos Int* 2016; 27: 1281–1386
- Schwartz GJ, Munoz A, Schneider MF *et al.* New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009; 20: 629–637
- Lalayiannis AD, Crabtree NJ, Ferro CJ *et al.* Routine serum biomarkers, but not dual-energy X-ray absorptiometry, correlate with cortical bone mineral density in children and

- young adults with chronic kidney disease. *Nephrol Dial Transplant* 2021; 36: 1872–1881
11. Flynn JT, Kaelber DC, Baker-Smith CM et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017; 140: e20171904
 12. Lurbe E, Agabiti-Rosei E, Cruickshank JK et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens* 2016; 34: 1887–1920
 13. Touboul PJ, Hennerici MG, Meairs S et al. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis* 2012; 34: 290–296
 14. Jourdan C, Wuhl E, Litwin M et al. Normative values for intima-media thickness and distensibility of large arteries in healthy adolescents. *J Hypertens* 2005; 23: 1707–1715
 15. Doyon A, Kracht D, Bayazit AK et al. Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. *Hypertension* 2013; 62: 550–556
 16. Engelen L, Bossuyt J, Ferreira I et al. Reference values for local arterial stiffness. Part A: carotid artery. *J Hypertens* 2015; 33: 1981–1996
 17. Diaz A, Bia D, Zócalo Y et al. Carotid intima media thickness reference intervals for a healthy Argentinean population aged 11–81 years. *Int J Hypertens* 2018; 2018: 8086714
 18. Agatston AS, Janowitz WR, Hildner FJ et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15: 827–832
 19. Devereux RB, Alonso DR, Lutas EM et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57: 450–458
 20. Khoury PR, Mitsnefes M, Daniels SR et al. Age-specific reference intervals for indexed left ventricular mass in children. *J Am Soc Echocardiogr* 2009; 22: 709–714
 21. de Simone G, Daniels SR, Kimball TR et al. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. *Hypertension* 2005; 45: 64–68
 22. Kracht D, Shroff R, Baig S et al. Validating a new oscillometric device for aortic pulse wave velocity measurements in children and adolescents. *Am J Hypertens* 2011; 24: 1294–1299
 23. Thurn D, Doyon A, Sözeri B et al. Aortic pulse wave velocity in healthy children and adolescents: reference values for the vicorder device and modifying factors. *Am J Hypertens* 2015; 28: 1480–1488
 24. Diaz A, Zocalo Y, Bia D et al. Reference intervals and percentiles for carotid-femoral pulse wave velocity in a healthy population aged between 9 and 87 years. *J Clin Hypertens* 2018; 20: 659–671
 25. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010; 31: 2338–2350
 26. Civilibal M, Caliskan S, Adaletli I et al. Coronary artery calcifications in children with end-stage renal disease. *Pediatr Nephrol* 2006; 21: 1426–1433
 27. Oh J, Wunsch R, Turzer M et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation* 2002; 106: 100–105
 28. Mitchell JD, Paisley R, Moon P et al. Coronary artery calcium and long-term risk of death, myocardial infarction, and stroke: the Walter reed cohort study. *JACC Cardiovasc Imaging* 2018; 11: 1799–1806
 29. Bashir A, Moody WE, Edwards NC et al. Coronary artery calcium assessment in CKD: utility in cardiovascular disease risk assessment and treatment? *Am J Kidney Dis* 2015; 65: 937–948
 30. Karras A, Haymann JP, Bozec E et al. Large artery stiffening and remodeling are independently associated with all-cause mortality and cardiovascular events in chronic kidney disease. *Hypertension* 2012; 60: 1451–1457
 31. Townsend RR, Anderson AH, Chirinos JA et al. Association of pulse wave velocity with chronic kidney disease progression and mortality: findings from the CRIC study (Chronic Renal Insufficiency Cohort). *Hypertension* 2018; 71: 1101–1107
 32. Azukaitis K, Jankauskiene A, Schaefer F et al. Pathophysiology and consequences of arterial stiffness in children with chronic kidney disease. *Pediatr Nephrol* 2021; 36: 1683–1695
 33. London GM, Pannier B. Arterial functions: how to interpret the complex physiology. *Nephrol Dial Transplant* 2010; 25: 3815–3823
 34. Laurent S, Boutouyrie P, Asmar R et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37: 1236–1241
 35. Kozel BA, Danback JR, Waxler JL et al. Williams syndrome predisposes to vascular stiffness modified by antihypertensive use and copy number changes in NCF1. *Hypertension* 2014; 63: 74–79
 36. Briet M, Bozec E, Laurent S et al. Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int* 2006; 69: 350–357
 37. London GM. Arterial stiffness in chronic kidney disease and end-stage renal disease. *Blood Purif* 2018; 45: 154–158
 38. Ohyama Y, Ambale-Venkatesh B, Noda C et al. Association of aortic stiffness with left ventricular remodeling and reduced left ventricular function measured by magnetic resonance imaging. *Circulation Cardiovasc Imaging* 2016; 9: e004426
 39. Tawadrous H, Kamran H, Saliccioli L et al. Evaluation of arterial structure and function in pediatric patients with end-stage renal disease on dialysis and after renal transplantation. *Pediatr Transplant* 2012; 16: 480–485
 40. Mitsnefes MM, Kimball TR, Witt SA et al. Left ventricular mass and systolic performance in pediatric patients with chronic renal failure. *Circulation* 2003; 107: 864–868
 41. Chinali M, Matteucci MC, Franceschini A et al. Advanced parameters of cardiac mechanics in children with CKD: the 4C study. *Clin J Am Soc Nephrol* 2015; 10: 1357–1363
 42. Mitsnefes MM, Pierce C, Flynn J et al. Can office blood pressure readings predict masked hypertension? *Pediatr Nephrol* 2016; 31: 163–166
 43. Safar ME. Arterial stiffness as a risk factor for clinical hypertension. *Nat Rev Cardiol* 2018; 15: 97–105